

Treatment with Calcineurin Inhibitors of Oral Lichen Planus. An Attempt to Clarify the Issue.

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Received date: March 20, 2018; Accepted date: April 7, 2018; Published date: April 11, 2018

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Abstract

After a FDA warning, dermatologists are concerned about a potential cancer risk inherent to the use of topical calcineurin inhibitors and increasingly reluctant to prescribe them. Yet those drugs have proved to be extremely active in atopic dermatitis and erosive lichen planus, to mention some of the responsive skin disorders. The results derived from the survey of the literature are exceedingly contentious and prevent any definite conclusion to be drawn, also in consideration that the alternative therapies for both diseases are also, if not more, dangerous and that lichenoid features are common in oral premalignant and malignant lesions. Diagnostic flaws are possible even for expert pathologists. The author believe that patients with erosive lichen planus should be immediately biopsied and topical calcineurin inhibitors prescribed to ameliorate the severe impairment of the quality of life. Patients should be constantly monitored and never abandoned to self-therapy.

Keywords: Calcineurin inhibitors; Lichen planus; Mucosal diseases; Pimecrolimus; Topical steroids; Non-melanoma skin cancers; Oral mucosa; Atopic dermatitis

Review

Thirteen years ago, the FDA issued a public health advisory to inform health care providers and patients about a potential cancer risk from use of Elidel cream (pimecrolimus) and Protopic ointment (tacrolimus) [1]. The FDA concern was based on information from animal studies, case reports in a small number of patients, and how these drugs work. With that warning in mind, dermatologists are increasingly reluctant to prescribe the two drugs when they are dealing with skin disorders involving vast areas of the skin or with mucosal diseases.

Yet, calcineurin inhibitors in topical preparation have proved to be extremely active in dermatological diseases, like atopic dermatitis, and in several mucosal disorders that go from geographical tongue [2] to pemphigus vulgaris [3]. A huge literature is available. In this essay I will refer mainly to the most recent reviews.

Efficacy of Topical Preparations

Several papers deal with oral erosive lichen planus (ELP). In ELP, long-term efficacy of either tacrolimus or pimecrolimus has been reported in no less than 264 patients. Although one Cochrane systematic review concluded that there is insufficient evidence to support the effectiveness of any specific treatment as being superior [4], another systematic review of 5 double-blind studies, 1 investigator-blinded study, 10 open prospective studies, 6 retrospective studies, and 28 case reports concluded that there is strong evidence to suggest that the use of pimecrolimus 1% cream is superior or equally efficacious as traditional therapies for ELP. For vulvovaginal lesions pimecrolimus was superior to placebo in one double-blind study, and tacrolimus proved effective in open studies [5].

Lesions, however, relapse following suspension of the drug and long-term treatment is usually needed. Obviously, possible serious adverse effects are of concern.

Adverse Effects

Systemic cancerogenicity

Most authors believe that the side-effects are limited, and that no serious toxicities have been documented [6]. The results of case reports, literature surveys and Cochrane systematic reviews are highly controversial, however. In a recent survey, Cai et al. found 880 cases of cancer in 66,176 patients (1.3%) from 2004 to 2012. The adjusted HRs for overall malignancy were 0.82 (95% CI: 0.44–1.39) for tacrolimus-exposed and 1.30 (95% CI: 0.59–2.45) for pimecrolimus-exposed patients. Subgroup analysis of the tacrolimus-exposed pediatric patients (≤ 16 years) showed a significant association between tacrolimus use and B-cell leukemia: HR 26.4 (95% CI: 4.77–146) [7]. In another study, the age and sex hazard ratio for T-cell lymphoma was 5.44 (95% CI: 2.51 to 11.79; $p < 0.001$) for tacrolimus and 2.32 (95% CI: 0.89 to 6.07; $p = 0.086$) for pimecrolimus [8].

On the other hand, in a 5-year long recent study on children with mild-to-moderate atopic dermatitis, Sigurgeirsson et al. found no malignancies at all, but only benign adverse effects [9]. Arellano et al. observed as well that the number of malignancies and lymphomas among tacrolimus-exposed patients is much lower than in the general population [10], even though they found that severity of AD was the main factor associated with an increased risk of lymphoma, a fact that suggests that calcineurin inhibitors are being used extensively. Likewise, the number of malignancies and lymphomas observed in children treated with either tacrolimus or pimecrolimus and followed for up to 5.5–6.5 years is similar to that expected in the general population [11]. Lastly, reviewing the literature, Legendre et al. found that in cohort studies, the risk of lymphoma was slightly increased (RR: 1.43 (95% CI: 1.12–1.81)), but not in case-control studies (OR: 1.18

(95% CI: 0.94-1.47)). Again, severity of AD was a significant risk factor and highly potent topical steroids were associated with an increased risk of lymphoma [12].

As severity of a topic dermatitis, and therefore its extent, have been found to be a significant risk factor, crucial is the amount of the drug absorbed through the skin or through mucosae.

Absorption through the skin

Passeron et al. found in 14 patients with ELP that the blood concentrations of pimecrolimus were always above the threshold (mean value, 2.84 ng/mL; extreme values, 0-6.19 ng/mL) [13]. Yan et al. found, in Netherton syndrome, that pimecrolimus blood levels ranged from 0.625 to 7.08 ng/ml, in any case being much lower than expected even when applied to 50% of total body surface area [14]. According to Mc Caughey et al. in 9/10 of ELP subjects treated with pimecrolimus, the levels were consistently low. In another article, pimecrolimus blood levels were detected in 5/10 subjects and all stayed below 4 ng/mL [15]. In another article, Tacrolimus 0.1% was applied in 50 patients with ELP up to 39 months and its mean blood levels were low and even decreased with duration of therapy from 2.7 microg/l (week 1) to 0.5 microg/l (week 32) [16].

Animal studies revealed, however, that the concentration of tacrolimus in the lymph node draining the treated skin area is equal to that found in the lymph nodes of animals treated with oral tacrolimus, even though the serum concentration of tacrolimus was low [17].

To evaluate better the relevance of those concentrations, one should keep in mind that the trough levels of tacrolimus administered orally have even calculated to be fairly consistent at 7.9-18 ng-h/mL without variations with age or sex [18] and that, at such levels, lymphoma, non-melanoma skin cancers and melanomas have been consistently reported, related to the level of immunosuppression.

The inhibition of immune competent cells, which normally prevent malignancies to develop, is considered to be the main mechanism of tumorigenesis promotion. In particular, a reduction of the CD4/CD8 ratio has been found in the lymph nodes of mice treated with tacrolimus [19]. Even this issue is controversial, however. In fact, it has been shown that patients treated in such a way displays a normal immune response to vaccination [20], develop an adequate delayed hypersensitivity reaction as demonstrated by cases of contact dermatitis [21], and have an infection rate within the expected range given the predisposition of the patient with atopic dermatitis to cutaneous infections [11].

If systemic carcinogenicity of topical tacrolimus is still dubious, more evidence favors the local carcinogenicity.

Local carcinogenicity

The local carcinogenic potential of long-term topical tacrolimus application has been claimed. However, up to 2005, only 10 cases of skin tumors mostly affecting the area where the drug had been applied had been reported, consisting of squamous cell carcinoma, cutaneous sarcoma and malignant melanoma [22].

In fact, tacrolimus has also a direct carcinogenic potential promoting the transformation of initiated cells. Tacrolimus is used in ELP essentially for its capacity to augment apoptosis in T-cells, which are the main effectors in ELP, but tacrolimus inhibits apoptosis in non-lymphoid cells as well [22]. Tacrolimus leads to Erk activation in the

mucosal epithelium and inhibits the induction of p53, both being important cancer signaling pathways. Bax, which is a proapoptotic member of the Bcl-2 family and its transcription is directly regulated by p53, is reduced in epithelial cells of tacrolimus treated mucosa and even in carcinoma cells. Lastly, tacrolimus-binding protein FKBP 38 blocks apoptosis, binds to Bcl-2 and targets Bcl-2 to the mitochondria [23].

Lichen planus

ELP refers to the oral localization of a chronic disease, named lichen planus that usually affects the skin. Mucosal lesions may be atrophic or erosive and may involve the oral mucosa and the vulva and the penis as well. Lichen planus is an autoimmune disease in which CD4 and CD8 lymphocytes attack the keratinocytes of the basal layer of the epidermis and tend to destroy them. Interleukins IL-6 and IL-8 are released into the circulation and their blood level parallels the severity of the disorder as well as the efficacy of the treatment [24]. The erosion is caused by the particular aggressiveness of CD8 cells which destroy the entire epidermis. Ulcerations may also occur, depending on additional factors like trauma or infections.

Long standing erosion can result in squamous cell carcinoma. Cofactors may be tobacco smoking, alcoholism, coinfection with oncogenic types of human papilloma virus and HCV, and immunosuppression [25]. The possibility of immune suppression raises the issue whether a patient with ELP could be treated with topical tacrolimus. The problem is a difficult one, especially after the FDA warning. Blood levels should be diriment for the systemic carcinogenicity. From the oral mucosa the blood concentration of pimecrolimus absorbed is said to be 2.84 ng/mL as an average; extreme values ranging between 0-6 and 19 ng/mL) [13], quite close to 20 ng/ml, which is regarded as relatively safe for patients using oral tacrolimus after a kidney transplantation [26].

As for the local carcinogenicity, the problem could be resolved on the basis of the evaluation of the two levels of risk. Problem is that there is no consensus about the risk ELP patients bear. According to Becker, the average risk is 3.6-4.6%, the reported transformation rates varying from 0 to 9% [22], while according to Fitzpatrick the risk is only 1.09% [27] and to Agha-Hosseini et al. ranges from 0 to 37% with a mean of 4.59% [28]. Probably, this depends on the fact that the differential diagnosis between ELP and the epithelial dysplasia is not always easy: lichenoid features are frequent in oral premalignant and malignant lesions [28]. As for the treatment with topical tacrolimus, the risk is simply unknown. Up to 2006, Becker et al. reported 10 cases of cancer in mucosal lesions of lichen planus treated with tacrolimus [22]. Since then a few other cases have published.

On the other hand, ELP is an exceedingly distressing disorder, impeding speaking and eating, and emanating a fetid odor. Moreover, when it affects female genitals prevents any sexual activity. The quality of life is highly disturbed and deserves an adequate treatment.

Conclusions

Results derived from the survey of the literature are exceedingly contentious and prevent any definite conclusion to be drawn. The reader should not neglect, however, that some authors or coauthors are Novartis employees or have been funded by Novartis or Astellas (the dealers of Elidel and Protopic). The simple fact that the methods of evaluation of the blood levels of those drugs are not within reach of the common investigator should be a reason for thought.

Of course, dermatologists are concerned by the possible medico-legal consequences of the management of their patients, especially those with atopic dermatitis and ELP that need long-term treatments. On the other hand, alternative therapies for both diseases are also, if not more, dangerous. I believe that all ELP patients should be biopsied immediately and the pathologist alerted on the possibility that a squamous cell carcinoma is not already present or, as it is my own experience, mimics ELP. Diagnostic flaws are frequent [29,30] and such a possibility casts some doubts on the entire literature. The consequent therapy with topical calcineurin inhibitors can be initiated to ameliorate the severe impairment of the quality of life. Patients, however, should be constantly monitored and never abandoned to self-therapy.

References

1. Anonymous (2006) New warnings for two eczema drugs. U.S. Food and Drugs Administration.
2. Ishibashi M, Tojo G, Watanabe M, Tamabuchi T, Masu T, et al. (2010) Geographic tongue treated with topical tacrolimus. *J Dermatol Cas Rep* 4: 57-59.
3. Hodgson TA, Malik F, Hegarty AM, Porter SR (2003) Topical tacrolimus: a novel therapeutic intervention for recalcitrant labial pemphigus vulgaris. *Eur J Dermatol* 13: 142-144.
4. Thongprasom K, Carrozzo M, Furness S, Lodi G (2011) Interventions for treating oral lichen planus. *Cochrane Database Syst Rev* 6: CD001168.
5. Samyia M, Lin AN (2012) Efficacy of Topical Calcineurin Inhibitors in Lichen Planus. *J Cut Med Surg* 16: 221-229.
6. López-Jornet P, Camacho-Alonso F, Salazar-Sanchez N (2010) Topical tacrolimus and pimecrolimus in the treatment of oral lichen planus: an update. *J Oral Pathol Med* 39: 201-205.
7. Cai SC, Li W, Tian EA, Allen JC, Tey TL (2016) Topical calcineurin inhibitors in eczema and cancer association: A cohort study. *J Dermatol Treat* 27: 531-537.
8. Hui RL, Lide W, Chan J, Schottinger J, Yoshinaga M, et al. (2009) Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother* 43: 1956-1963.
9. Sigurgeirsson B, Ho V, Ferrándiz C, Andriano K, Grinienko A, et al. (2008) Effectiveness and safety of a prevention-of-flare-progression strategy with pimecrolimus cream 1% in the management of paediatric atopic dermatitis. Pimecrolimus 1% cream in (paediatric) Eczema: Prevention of Progression multi-centre investigator study group. *J Eur Acad Dermatol Venereol* 22: 1290-1301.
10. Arellano FM, Wentworth CE, Arana A, Fernández C, Paul CF (2007) Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 127: 808-816.
11. Siegfried EC, Jaworski JC, Hebert AA (2013) Topical Calcineurin Inhibitors and Lymphoma Risk: Evidence Update with Implications for Daily Practice. *Am J Clin Dermatol* 14: 163-178.
12. Legendre L, Barnette T, Mazereeuw-Hautier J, Meyer N, Murrell D, et al. (2015) Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: A systematic review and meta-analysis. *J Am Acad Dermatol* 72: 992-1002.
13. Passeron T, Lacour JP, Fontas E, Ortonne JP (2007) Treatment of oral erosive lichen planus with 1% pimecrolimus cream: a double-blind, randomized, prospective trial with measurement of pimecrolimus levels in the blood. *Arch Dermatol* 143: 472-476.
14. Yan AC, Honig PJ, Ming ME, Weber J, Shah KN (2010) The Safety and Efficacy of Pimecrolimus, 1%, Cream for the Treatment of Netherton Syndrome Results From an Exploratory Study. *Arch Dermatol* 146: 57-62.
15. McCaughey, C, Machan, M, Bennett, R (2011) Pimecrolimus 1% cream for oral erosive lichen planus: a 6-week randomized, double-blind, vehicle-controlled study with a 6-week open-label extension to assess efficacy and safety. *J Eur Acad Dermatol Venereol* 25: 1061-1067.
16. Hodgson TA, Sahni N, Kaliakatsou F, Buchanan JA, Porter SR (2003) Long-term efficacy and safety of topical tacrolimus in the management of ulcerative/erosive lichen planus. *Eur J Dermatol* 13: 466-470.
17. Niwa Y, Nasr I (2005) Are we starting to induce skin cancer in order to avoid topical steroids? *J Eur Acad Dermatol Venereol* 19: 387-389.
18. Naik P, Madhavarapu M, Mayur P, Nayak KS, Sritharan V (2012) Pharmacokinetics of tacrolimus in adult renal transplant recipients. *Drug Metabol Drug Interact* 27: 151-155.
19. Niwa Y, Terashima T, Sumi H (2004) Topical application of the immunosuppressant tacrolimus accelerates carcinogenesis in mouse skin. *Br J Dermatol* 149: 960-967.
20. Migita K, Akeda Y, Akazawa M, Tohma S, Hirano F, et al. (2015) Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tacrolimus. *Arthritis Res Ther* 17: 149.
21. Saitta P, Brancaccio R (2007) Allergic contact dermatitis to pimecrolimus. *Contact Dermatitis* 56: 43-44.
22. Becker, JC, Houben, R, Vetter, CS, Brocker, EB (2006) The carcinogenic potential of tacrolimus ointment beyond immune suppression: a hypothesis creating case report. *BMC Cancer* 6: 7.
23. Shirane M, Nakayama KI (2003) Inherent calcineurin inhibitor FKBP38 targets Bcl-2 to mitochondria and inhibits apoptosis. *Nat Cell Biol* 5: 28-37.
24. Vohra S, Singal A, Sharma SB (2016) Clinical and serological efficacy of topical calcineurin inhibitors in oral lichen planus: a prospective randomized controlled trial. *Int J Dermatol* 55: 101-105.
25. Aghbari SMH, Abushouk AI, Attia A, Elmarazy A, Menshawy A, et al. (2017) Malignant transformation of oral lichen planus and oral lichenoid lesions: A meta-analysis of 20095 patient data. *Oral Oncol* 68: 92-102.
26. Przepiorka D, Nash RA, Wingard JR, Zhu J, Maher RM, et al. (1999) Relationship of tacrolimus whole blood levels to efficacy and safety outcomes after unrelated donor marrow transplantation. *Biol Blood Marrow Transplant* 5: 94-97.
27. Fitzpatrick SG, Hirsch SA, Gordon SC (2014) The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. *J Am Dent Assoc* 145: 45-56.
28. Agha-Hosseini F, Sheykhbahaei N, SadrZadeh-Afshar MS (2016) Evaluation of Potential Risk Factors that contribute to Malignant Transformation of Oral Lichen Planus: A Literature Review. *J Contemp Dent Pract* 17: 692-701.
29. Fitzpatrick SG, Honda KS, Sattar A, Hirsch SA (2014) Histologic lichenoid features in oral dysplasia and squamous cell carcinoma. *Oral Surg Oral Med Oral Radiol Endod* 117: 511-520.
30. Raj AT, Patil S (2017) Diagnostic flaws in oral lichen planus and related lesions. *Oral Oncol* 74: 190-191.